REMARKS

Reconsideration is requested.

Claims 1 and 3-6 are pending.

Claim 1 has been revised, without prejudice, to further confirm that the lymphatic vessel system of the claims comprise lymphatic vessels, lymphatic sacs and a lymphatic heart. Support for the claim revision may be found, for example, on page 3, lines 12-14 ("Surprisingly, in transgenic tadpoles a truly developed lymphatic vascular network can be visualized comprising lymphatic vessels, lymphatic sacs and lymphatic hearts."). No new matter has been added.

To the extent not obviated by the above, the Section 103 rejection of claims 1 and 3-6 over Beck (Mechanism of Development, 1999, 88:221-227), Witte (Microscopy Research and Technique, 2001, 55; 122-145) and Bartel (Anat Embryol, 2000, 202:55-65), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following distinguishing comments.

The claimed invention provides an animal model to study, on a large scale, putative lymphangiogenic candidates (see for example, page 2, line 26-29 of the specification).

An easily reproducible animal model to study, on a large scale, putative lymphangiogenic candidates should possess a functional lymphatic vessel system, as claimed, which comprises lymphatic vessels, lymphatic sacs and lymphatic hearts (see page 3, lines 12-14 of the application).

The Examiner has previously correctly characterized Beck as not specifically teaching making transgenic Xenopus comprising GFP under the control of promoters specific for expression within the lymphatic system but instead describe a method of visualizing the pancreas, liver and small intestine. See page 5 of the Office Action dated March 14, 2008, The Examiner has also previously acknowledged that Beck fails to teach using a transgenic *Xenopus* to visualize the lymphatic vessel system or to screen for compounds capable of modulating lymphatic vessel development. Id.

Beck at al. are silent about a model of the lymphatic system and only describe a method of visualizing the pancreas, liver and small intestine. Beck fails to suggest using *Xenopus* as a model for the lymphatic system.

The Examiner has previously described Witte et al. as teaching that lymphatic vessel development is poorly understood and that Witte et al. teach the use of "mice and not *Xenopus as* models". Id. Witte et al describe "Experimental Models of Lymphvasculogene and Lymphangiogenesis" which include mouse, dog, sheep, and rat animal models. See pages 127-128 of Witte. Witte is a review article published two years after Beck as a review of the state of the art. At least twenty three (23) of the references listed in Witte et al were co-authored by the first author (i.e., MH Witte). The authors of Witte were apparently well skilled in the art and aware of the state of the art. The authors of the cited document conclude, in the section titled" LOOKING FORWARD AND BACKWARD Horizons in Molecular and Clinical Lymphangiogenesis", that "Therapeutic (and preventive) approaches can be developed and documented by organ-specific prevention (modification) of the lymphatic phenotype in transgenic and

other animal models and in patients." See page 139 of Witte et al. The cited art appears to suggest in this regard that sufficient animal models are available. Witte et al explains that future work should focus on refining and existing models. Specifically, Witte et al explains that

> "While more fully defining the normal "lymphatic phenotype" and delineating the abnormal phenotype in LE-AD patients and transgenic mice in terms of the specific lymphatic growth disturbance, the events surrounding "lymphatic failure" (reduced lymphatic absorption/absorptive capacity and lymphedema accumulation) also need to be addressed and quantitated. This analysis should provide a defined target to prevent, ameliorate, or reverse this imbalance. In the more chronic LE stage, "skin failure" and interstitial changes from lymph stasis in internal organs should become a further subject for detailed delineation and for gene/protein treatment to modify the physiologicalbiochemical abnormalities associated with long-standing lymph stasis." See paragraph spanning pages 139-140 of Witte et al.

Contrary to the Examiner's assertions, Witte et al provide no motivation to use *Xenopus* as a model in place of the mammalian models of Witte et al. The Examiner's comment regarding the alleged disclosure of page 129 of Witte et al relating to tadpoles is noted. The sentence of the Introduction of Witte et al however (i.e., "Indeed, when these lymph hearts are slowed or paralyzed, frogs quickly drown in their rapidly forming lymph.") refers to frogs, as opposed to tadpoles, and does not suggest the claimed invention or the use of tadpoles as a model of the functional lymphatic vessel system.

Finally, the applicants believe that Bartel et al. relates to the microvasculature of the lung in tadpoles. In fig. 4, page 59 the term 'lymphatics' is shown and on page 65, left column, 3rd paragraph 'the presence of lymphatic vessels' is indicated. Bartel et al is not believed to cure the deficiencies noted above with regard to Witte et al and Beck.

The applicants submit that the cited art fails to provide motivation for one of ordinary skill to have made the claimed invention. One of ordinary skill in the art would not have reasonably predicted or considered that a tadpole could be used as a model for the human lymphatic system and for studying lymphangiogenic candidates. Prior to the present invention, one of ordinary skill would not have reasonably predicted that tadpoles possessed a functional lymphatic vessel system, as required by the present claims. Moreover, one of ordinary skill in the art would not have reasonably predicted that it would have been possible to visualize a system comprising lymphatic vessels, lymphatic sacs and lymphatic hearts, as required by the present claims. See for example, Examples 1 and 2 on page 15-17 of the present specification where the lymphatic system of tadpoles is shown to comprise vessels (page 16, lines 5 and 11), a lymphatic heart (page 16, line 7) and vascular structures (page 16, line 6) and/or lymphatic sacs (page 16, line 34).

Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

Respectfully submitted,

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